IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: CLASSEN, John B.	)	Art Unit: 1643
Serial No.: 08/591,651	)	Examiner: BRUMBACK, B.
Filed: February 12, 1996	)	Washington, D.C.
For: METHOD AND COMPOSITION FOR AN EARLY VACCINE...	)	October 17, 2002
	)	Docket No.: CLASSEN=1A

#44 Decl. w/ attach. 10/24/02

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

DECLARATION (II) OF DR. BART CLASSEN

I, J. Barthelow ("Bart") Classen, hereby declare as follows:

1. I am the sole named inventor of the above-identified application. I received a B.S. in Zoology, summa cum laude, from the University of Maryland in 1983, and my M.D. from the University of Maryland School of Medicine in 1988. I worked 3 years at NIH as an immunologist in the laboratory of immunology, NIAID. I am a Licensed Physician in Maryland, Delaware, District of Columbia, Virginia, and West Virginia. I have conducted extensive experimental and epidemiological studies of the relationship of autoimmune diseases to immunization.

The above-identified application, and its predecessors, arose from my work, in particular, my recognition that the timing of first immunization) affected the incidence of diabetes in humans, NOD mice, and BB rats, and of SLE in a mouse model. Generally speaking, early immunization (prior to 42 days of age) decreased the incidence, and late immunization (after 42 days of age) increased it.

2. In the course of prosecution, the Examiner has questioned enablement for the claims of the above-identified application with regard to methods and compositions for reducing the incidence of diabetes in humans.

3. The Examiner is aware that the claims are supported by both veterinary and epidemiological evidence. She discounts the animal studies because she does not believe it to be safe to extrapolate from animals to humans.

It should first be noted that Applicant is extrapolating from experience with several species of animals, not just one. While Applicant's initial showing was in NOD mice, Applicant later performed a successful confirmatory experiment with BB rats. BB rats have an immunologically distinct disease from the disease in NOD mice. Nonetheless, both spontaneously develop diabetes at an early age, and both responded favorably to early immunization as taught by Applicant. NOD mice and BB rats are accepted animal models of human diabetes. Moreover, Applicant has shown that early immunization decreases the risk of SLE in MRL-lpr mice, an accepted SLE model.

The Examiner has questioned the extrapolation from rodents to humans "because of the criticality of the age of administration of the immunogens and the difference in maturation rates between rodents and humans" (OA February 21, 2001, §6, para. bridging pp. 8-9).

The issue of maturation rates is discussed in the specification. It is not the overall maturation rate which is important, just the rate of maturation of the immune system.

The specification states at page 27, lines 15-23:

> The immune systems of mice and men mature at comparable rates, with both species capable of mounting immune responses to vaccine antigens by the time the recipients are several months

> old. A comparison of the experimental and epidemiological examples in this specification supports this conclusion. Subtle differences in the rates of development of the immune systems of mice and humans may be detected however using a broad range of assays including in vivo assays, in vitro assays, in vitro assays and phenotypic cell assays.

It then discusses the appropriate assays in detail, at page 27, line 24 to page 29, line 12, and concludes at page 29, lines 13-19:

> The present invention therefore can include administration of the immunogens to humans when said humans' immune systems are in a state of maturation and responsiveness comparable to that of mice or rats at the times indicated above, in such circum-stances as it would be less effective to administer those immunogens to humans at the same chronological ages as they were administered to mice or rats.

Mice develop faster than humans. If we give a dose of vaccine before 42 days of age in mice, and it reduces the incidence or severity of diabetes, then giving the same vaccine at the same time to humans should also be effective, because, at the same age, the human will be at an even earlier stage of maturation than the mouse. In our examples, the day of first administration was day 8 in Example 1, day 1 in Example 2, day 10 in Example 3, day 1 in Example 4 (rate), and day 1 in Example 5. Even day 8 in the mouse will certainly correspond to a very young human.

Finally, it should be recognized that Applicant's animal data cannot be viewed in isolation; the epidemiological data serves to confirm the finding in mice and rats and justify the questioned extrapolation.

4. The Examiner says that "epidemiological data alone does not establish a causal relationship". That is true, but it can render a proposed utility believable.

The scientific community often must rely on epidemiological data to establish causation. It is unethical to perform a clinical trial with a suspected toxic substance in order to "prove" the substance is toxic. Therefore epidemiology data alone is suffice to establish casual relationship for practical purposes. For example no one has ever done a prospective study to establish that cigarettes cause disease. The establishment of a casual relationship between cigarettes and disease is based on epidemiology data. The same goes with almost all toxins, for example asbestos, carcinogenic chemicals, radiation, toxic chemicals.

5. The Examiner also relies on opposing epidemiological studies. In so doing, he has cited both references which present alternative interpretations of the same study population, and references which study other populations. However, these alternative interpretations and studies are marred by various flaws, which, in my opinion, compel the conclusion that they do not rebut the conclusions which I have reached.

6. I believe that it is desirable to place before the Examiner a comprehensive overview which (1) sets forth my own epidemiological studies, and answers any criticisms made of them in the art of record, and (2) sets forth the epidemiological studies relied on by the examiner, and explains their deficiencies.

7. Some of my epidemiological studies are set forth in the specification. Others have been presented in articles published

since the filing date. While some of these articles may already have been made of record, for ease of consideration in conjunction with this Declaration, copies of all of the articles cited herein have been bound with this Declaration. It is requested that they be made of record.

8. The Examiner's attention is first directed to Table 1 of this Declaration, which lists my own epidemiological studies, as well as one new study by another (Sanjeevi, copy enclosed) which has reached conclusions which support this application. This declaration incorporates by reference my own epidemiological studies which are listed in that Table.

9. The attention of the Examiner is then directed to Table 2 of this Declaration, which is a critique of the epidemiological studies, and secondary commentaries, cited by the Examiner. Table 2 cites a number of re-analyses which I have made of some of the datasets in question. Copies of these re-analyses, whether published or not, are enclosed, and are incorporated by reference into this declaration.

10. In considering Table 2, the Examiner should be aware of a pervasive problem with these studies, which is that most of them were obviously "underpowered" to identify as statistically significant a true difference between early vaccinated and unvaccinated groups, or between late vaccinated and unvaccinated groups, of the magnitude suggested by my own epidemiological studies.

A study is designed to test a hypothesis, e.g., that immunization with a particular immunogen at a particular time affects the incidence of diabetes. In performing statistical significance

tests, it is initially assumed that the study hypothesis is false, i.e., that there is no true difference between the larger populations represented by the study groups. This assumption is called the null hypothesis. Two types of error are recognized by statisticians.

A type I error arises when the study hypothesis is falsely accepted (and the null hypothesis falsely rejected). The significance, or P value, of a study is the probability of a type I error. It is conventional in the scientific community to consider P values of 0.05 or less to indicate the existence of a significant difference between the groups.

The converse error is a type II error; it arises when the study hypothesis is falsely rejected (and the null hypothesis falsely accepted). The smaller the number of individuals in the study, and the smaller the effect being looked for, the more difficult it is to produce data adequate to reject the null hypothesis.

The statistical power of a study is defined as the probability that a type II error will not occur. Most investigators would like the power to be at least 90%, that is, the probability of failing to demonstrate the statistical significance of a true difference to be 10% or less.

In a case-control study, the outcome is already known, e.g., the cases are diabetics and the controls are normals. One retrospectively compares the relative exposure of the cases and controls to a hypothesized risk factor, such as Hib immunization. If there is a difference in exposure, implying a difference in relative risk, the statistical significance of this difference is tested.

The problem with the use of a case-control study to ascertain the riskiness of vaccination is that the percentage of both cases and controls who are vaccinated (the "uptake" or "utilization" of

the vaccine) is high. If a case and a control received the same treatment, e.g., vaccination, they provide no information concerning differences between treatments. If most of the population has been immunized, most case-control pairs will be concordant, and the number of cases and controls necessary to give the study a given statistical power will be much higher.

Thus, for an unmatched case-control study, if we make the assumption that 90% of the controls were immunized, and that immunization produces a relative risk of 1.15, then, if the number of cases and controls is equal, the study would need 9,621 controls and 9,621 cases to reach a power of 80%.[1] If there were three times as many cases as controls (remember, diabetes is a relatively rare disorder), the same power (80%) would require 19,452 controls and 6,484 cases. To raise the power to 90% would necessitate 25,788 controls and 8,596 cases.[2]

Attached hereto and incorporated by reference herein is a tabulation of required case and control sizes for various values of significance, power, case: control ratio, relative risk, and uptake (% NOT ILL group vaccinated).

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[1] Even if the relative risk were 1.30, to achieve 80% power would require 2,919 cases and 2,919 controls.

[2] These calculations use software (Eoi Info 6, by CDC and WHO) implementing the formulae set forth in Fleiss, Statistical Methods for Rates and Proportions, pp. 38-45 (Wiley, 2d ed., 1981).

Table 1: Epidemiological Studies with Conclusions favorable to Applicant

(Left col. description of study and its findings; right col. description of any critiques, and applicant's rebuttal.)

1. Pertussis/BCG/Hib, Western Europe Classen Ex. 101 and Table I; see also Classen and Classen, "The Timing of Pediatric Immunization and the Risk of Insulin-Dependent Diabetes Mellitus", Infectious Diseases in Clinical Practice (IDCP), 6: 449-54 (1997), Table 2.	
incidence of diabetes correlated to immunization schedule for Western european countries in period 1980-1990, i.e. (1) no pertussis, no BCG (16.6), (2) pertussis, BCG before two months (7.4), (3) pertussis, but no BCG (10.92), (4) pertussis, BCG vaccination at school age (19.02), and (5) pertussis, BCG, Hib vaccination at 3 months and at school age (42.9). **There were highly significant differences in incidence between several groups**	The examiner has not pointed out any methodological flaws in this analysis, or cited any papers which do so. The examiner did cite PIDJ, which alluded to intercountry analyses by Moulton and LaPorte (see below)

2. Hib/MMR, Finland, 1970-1989 Classen pp. 93-95, see also Classen and Classen, IDCP (1997), table 3.	
changes in the incidence of diabetes were correlated to changes in immunization schedule in Finland, namely, (1) a large clinical trial (130,000) started Nov. 1974, of Hib or meningococcal polysaccharide vaccines, (2) increase in the antigenicity of the pertussis vaccine in 1976, (3) addition of measles, mumps and rubella in 1982, and (4) another large Hib vaccine clinical trial (114,000) initiated in Jan. 1986, and (5) addition of Hib to standard schedule in Jan. 1988. Data were stratified into periods 1970-76, 1977-79, 1980-82, and 1987-89, and into 0-4, 5-9 and 10-14 years old age groups. Large percent increases in incidence were seen in the two younger age groups in 1977-79, and in 1987-89. **The differences in incidence from one period to the next were significant, in some cases highly so.**	The examiner has not pointed out any methodological flaws in this analysis, or cited any papers which do so. The examiner did cite PIDJ and other papers which address Classen's analysis of the effect of a specific Hib trial in Finland, see below.

3. Pertussis/mumps/Hib; Allegheny County, Pennsylvania, 1965-1989 Classen pp. 95-97	
Changes in the incidence of type I diabetes were correlated with the changes in the immunization schedule in this county: (1) 1975 Pennsylvania legislation implying that pertussis immunization was not necessary; (2) increased pertussis immunization following a 1982 epidemic; (3) state law requiring mumps vaccination (1983); and (4) addition of Hib vaccine (polysaccharide in 1985, conjugated vaccine in 1987). Data were stratified into periods 1965-69, 1970-74, 1975-79, 1980-84, and 1985-89. The incidence decreased in 1975-79 (-59%) and increased in 1980-84 (276%) and 1985-9 (63%). These three changes were highly significant.	The examiner has not pointed out any methodological flaws in this analysis, or cited any papers which do so. No papers providing contradictory new data for the county have been cited.

4. Smallpox; Netherlands Classen p. 97, L8-14; P98, L12-P99,L4; Table IV; Classen and Classen, "Immunization in the First Month of Life may Explain Decline in Incidence of IDDM in The Netherlands," Autoimmunity, 31: 43-5 (1999)(Ex. 5A).	
The practice in the Netherlands during 1960s was to immunize for smallpox at 2 months of age during non-epidemic conditions and earlier (perhaps at birth) during epidemics. The Classen appl. reports that cohorts born during smallpox epidemics had a lower incidence of type I diabetes then those born at other times. The implication is that **early** administration of the smallpox immunogen **reduced** the incidence of diabetes. **Table IV** Correlates cumulative rate of incidence of type I diabetes in Dutch[3] military recruits with the number of smallpox cases in Europe in the year of birth of the recruit, for the period 1960-1970. There was a statistically significant decline in 1962, which was the year of a smallpox epidemic. There was also a decline in another epidemic year, 1966, but this decline was not statistically significant. Classen concludes that the declines were attributable to changes in immunization practice in response to the epidemic.	The examiner has not commented on this observation. The examiner generally cites PIDJ, which in turn cites Blom (see Table 2A below). The Blom study considered smallpox immunization in Sweden, observing a RR of 1.07 (conf. 0.77-1.49) . While the noted effect (while consistent in direction and magnitude with Classen's studies), was not statistically significant, at the time of the Blom study (cases reported in 1985-86), smallpox had long been excluded from the general Swedish vaccination program. The power of the study to detect the effect of smallpox immunization was therefore low.

[3] Mislabeled as "Danish" military recruits in Table IV and on page 97 of the specification. We are filing a supplemental amendment to correct this. The error is evident from inspection of the primary source, Drykoningen, et al., "The incidence of male childhood type 1 (insulin-dependent) diabetes mellitus is rising rapidly in the Netherlands, Diabetologia, 35: 139-42 (1992)(copy enclosed) cited at the bottom of Table IV. The number of diabetes cases is plainly taken from an article on the incidence of diabetes in **Dutch** military recruits.

5. BCG. Sweden Classen and Classen, IDCP (1997), Table 1	
BCG was routinely administered at birth to all newborns in Sweden until April 1975. The cumulative incidence of diabetes in the 1973-77 birth cohorts was studied. The difference between (1976-77) and (1973-74) was 32.2, with a one-tail P value of .0363. The difference beween 1974 and 1976 was 48.64, with a one tail P value of .0028. Classen used a one-tailed test because, based on his ealier epidemiological studies, he expected BCG at birth to decrease the risk of diabetes. However, the 1974/1976 comparison would have resulted in a finding of high significance even with a two-tailed test (P then .0056). Thus, early immunization with BCG was associated with a lower incidence of diabetes in later life, as compared to unvaccinated controls.	The examiner has not commented on this observation. The examiner cites PIDJ, which in turn cites Blom. Blom (1991) (see below) table 3 reported an odds ratio of 1.04 (conf 0.77-1.4) for tuberculosis immunization. Blom looked at 0-14 yr old diabetes cases reported in 1985-86, but BCG was mandatory only til 1975. So Blom's cases were either children who developed the diabetes relatively late, or younger children considered to be high risk for tuberculosis who received voluntary BCG immunization. In applicant's study, the cohort sizes were 95,000-109,000. Blom's evaluation of the effect of tuberculosis vaccination was certainly based on a smaller number of cases. Hence, it is not surprising that he had a broad confidence interval.

6. Hepatitis B, New Zealand Classen and Classen, IDCP (1997), Table 4; Id., "Diabetes Epidemic Follows Hepatitis B immunization program," New Zealand Med. J., 109: 195 (1996).	
Classen presents data on the incidence of type I diabetes in Christchurch, New Zealand, 1982-1991. A massive hepatitis B immunization program was introduced in 1988, with first immunization generally starting after 6 weeks from birth. Initially, children under 5 were immunized, but the program was externed over the next few years to include children under 16, with an acceptance rate of over 70%. The incidence of diabetes rose from 11.2 cases/100,000 in 1982-87 to 18.1/100,000 in 1989-91 (P=.0008). Classen attributes this highly significant increase to the late hepatitis B immunization.	Willis et al., 1997 (cited in PIDJ) question the published association between the hepatitis b vaccine and the development of IDDM in New Zealand. They analyzed the incidence of IDDM in children born before February 1988 to children born after this time. Their analysis was flawed for two reasons. First it assumed those born prior to 1988 did not receive hepatitis B vaccine. In fact there was a massive catch-up program in New Zealand with the hepatitis B vaccine originally given just to all preschool children (Gunn, 1989) but soon expanded so that all the children under the age of 16 received the hepatitis B vaccine, not just those born after 1988. The acceptance rates were estimated to be above 70% (Personal communications, Dr. Harry Nicholls, Senior Advisor for Communicable Diseases, Ministry of Health, Wellington, NZ). Thus children born in the 1970s and early 1980s received the hepatitis B vaccine. Second the incidence of IDDM differs depending on the age of the child in most countries including New Zealand, with fewer cases of IDDM occurring in ages 1-5 versus 10-14 (Scott et al., 1992) . Willis' analysis only proves that the incidence of IDDM is higher in

	older children (those born before 1988) than the very young children (those born after 1988). Petousis-Harris (ref. HE) admit that there was a rise of IDDM following hepatitis B vaccine in the North Island of New Zealand. They say an rise in IDDM was expected. There is a clear contradiction in the New Zealand Public Health Department's statements. First Poutasi (1996) denies there is a rise of IDDM in the North Island following the introduction of HepB. Once they had to admit a rise in IDDM occurred Clearly the rise was not expected or they would have stated that first.
7. Hib, Finland, 1983-87 Classen and Classen, "Clustering of Cases of Insulin Dependent Diabetes (IDDM) Occurring Three Years After Hemophilus Influenza B (Hib) Immunization Support Causal Relationship Between Immunization and IDDM", Autoimmunity, 35(4):247-53 (2002);[4] Classen and Classen, "Association between type 1 diabetes and Hib vaccine: causal relation is likely", BMJ 319:1133 (10/23/99)(Ex. 5C)	
This study had both prospective and retrospective aspects. All children born in Finland 10/1/85-8/31/87 (~116,000) were randomized to receive either (1) 4 doses of a Hib vaccine (at 3, 4, 6 and 18 mos.) or (2) one dose at 24 months. In addition, (3) the 128,500 children borne in children in the 24 prior months, who did not receive any Hib vaccine, were used as a historical control. Epidemiology: Comparing the treatment groups to the historical controls, it found that the cumulative	Karvonen et al., 1999 (ref. EV) concluded that the Hib vaccine was unlikely to cause IDDM. However their analysis was severely flawed They compared groups receiving 4 doses to 1 dose and groups receiving 1 dose to 0 doses. This analysis minimizes the difference and misleads the reader.Most objective researchers would compare the group receiving 4 doses to the group receiving 0 doses. Alternatively they would compare the combined vaccinated groups to the

[4] Previously made of record as unpublished manuscript.

incidence was significantly higher for the 4 dose group than for the control for the 0-7 (two-tailed), 2-7 (one-tailed), 5-7 (same), and (0-10)(same) age groups. The cumulative incidence of IDDM/100,000 in the 3 groups were 261, 237, 207 at 7 years and 398, 376, 340 at 10 years of age respectively. The relative risk at 7 years was 1.26. It was also significantly higher for the 1 dose group than the 0 dose group for the 5-7 (one-tailed) age group. See table 1.

Prospective study: In addition, clustering of cases is seen when the cumulative incidence is plotted against the age at diagnosis. Such clustering is seen even when the two treatment groups are compared, see Fig. 1(a). The curves separate at about 39 months of age and then become parallel. Analysis of this cluster reveals that the curves separate by about 20 cases/100,000 during a span of about 6 months, with a relative risk of 2.25 (p=0.04), see P250, col. 1.

group receiving 0 doses. Both reach statistical significance. Note that both regimens are contrary to the teachings of the Classen application (first admin should be before 42 days after birth).

The cumulative difference in cases IDDM/100,000 between those receiving 4 doses and those receiving 0 doses is 54 cases (P=0.013) at 7 years and 58 cases at 10 years (P=0.029) using a single tail Fisher test. The relative risk equals 1.26 at 7 years. The cumulative difference between those receiving 4 or 1 doses and those receiving 0 doses is 42 cases (P=0.016) at 7 years and 47 cases at 10 years (P=0.028).

Karvonen et al. did not analyze the clustering of cases.

Jefferson (ref. HP) questioned Classen's "unpublished reanalysis" of the Finnish data which Jefferson et al. presented at the NIH workshop. That data is now published in a peer-reviewed journal. Jefferson's own analysis is that published in Karvonen (ref. EV) and hence ref. HP adds nothing to ref. EV. The same is true for Bedford (ref. HD).

8. BCG, Southern India Sanjeevi, et al., Ann. N.Y. Acad. Sci. 958: 293-6 (2002)	
Sanjeevi examines the effect of BCG immunization on the incidence of diabetes in Southern India. Table 1 relates to the frequency of autoantibodies in BCG-vaccinated and nonvaccinated diabetic patients; of 137 diabetics (identified by GAD65 and IA-2 (CA512) autoantibodies), 86 were vaccinated with BCG **immediately after birth**, while the remaining 51 had not received BCG at all. Hence, based on Classen's work, it would be expected that BCG immunization would decrease the risk. This was indeed what Sanjeevi observed. The frequency of these autoantibodies was significantly (P <0.0005 for GAD65, <0.001 for ICA512) decreased in BCG-vaccinated diabetics (compated to those not vaccinated with BCG. (36% vs. 67% for GAD65, 19% vs. 43% for ICA512), see Table 1. Table 2 is limited to **type 1** diabetes patients. The frequency of the two antibodies was again significantly (P<.001) decreased decreased in the BCG vaccinated subjects (54% vz. 100% for GAD65; 23% vs. 62% for ICA512). Sanjeevi, who has no association with Classen, concludes that "BCG vaccination has an immunomodulatory role and is associated with decreased autoantibody positivity in south Indian diabetic patients, which is in conformity with the observations from animal models of autoimmune diabetes."	This a new reference. However, it should be noted that it is the first study specific to India.

9. Anthrax, U.S. Armed Forces[5] Institute of Medicine, *The Anthrax Vaccine: Is It Safe? Does It Work?* (March, 2002), available online from the National Academy Press, http://www.nap.edu/books/0309083095/html/	
Anthrax vaccine was given to 150,000 service members deployed for the Gulf War (1991). Later, DOD announced a plan for the mandatory vaccination of all U.S. service members. The program (AVA) began in March, 1998 with personnel sent to high-risk areas, such as South Korea and Southwest Asia. The vaccine is administered in a series of six subcutaneous injections. Obviously, the first administration was no earlier than the minimum age for military service. The Classen claims are supported by the IOM data for vaccinated service members (Table G-1). Each member's pre-vaccination service time served as control for that member's post-vaccination service time. The data in Table G-1 was based, as Table 6-4 notes, on 738,382 person-years post-vaccination and 478,093 person-years pre-vaccination. As shown in Table G-1, service members immunized with anthrax vaccine exhibited a significantly higher relative risk (3.46, 95% confidence limit of 1.51-7.90) of diabetes mellitus, post- vs. pre-vaccination. Table 6-4 says, "Of 843 diagnoses, adjusted RR significantly lowered for 12 diagnoses and	The report acknowledges that this study, with its "comparison of rates of hospitalization in the same individual before and after receipt of AVA removes many of the biases inherent in comparing groups vaccinated with AVA and groups not vaccinated with AVA." (P. 163). However, it argues that for diabetes, "it is possible for the rate before vaccination with AVA to be artificially and differentially lower since those who had the disease and who had been hospitalized for it would be less likely to be deployed and therefore less likely to be vaccinated." (P. 163). It also asserts that since the ratio of the rate of hospitalization for diabetes before vaccination with AVA (in those ultimately vaccinated) to the rate of hospitalization for diabetes in those never vaccinated (0.12, CI 0.06-0.24)(P. 169) is much lower than the overall hospitalization rate ratio of 0.63(P. 166), that this"supports the conclusion that there is no increased risk attributable to AVA."(PP. 164, 168-9)

[5] This reference presents several studies, one of which reports that vaccination significantly increases the risk of diabetes, and others which do not. The favorable study is discussed here and the other studies in Table 2A.

significantly elevated for 15 (see Appendix G, Table G-1). Diagnoses with significantly elevated adjusted RR (95% CI) include ... Diabetes mellitus...." It was one of three diagnoses singled out by this table.

The rise in diabetes rates post-immunization relative to pre-immunization was also found to be statistically significant in both men and women: "In examining the results stratified by sex, they are completely consistent. Yet there is only a 1 in 400 probability (0.05 x 0.05) that the results could be significant for both men and women independently by pure chance." P.168)

The pre/post immunization study was conducted **because** there was concern that it was inappropriate to compare vaccinated and unvaccinated personnel; the vaccine was given to personnel being deployed overseas, and these were considered to be generally healthier than the average military personnel. The finding that the pre-immunized group had a significantly lower hospitalization rate than the never-immunized group shows that this concern was **justified**. The latter were less healthy and therefore more likely to develop diabetes. Thus, an immunized vs. never-immunized study would tend to **underestimate** the risk of immunization.

This effect would be especially prominent in the case of diabetes. diabetes is an age-dependent disease, with the number of cases increasing with age. Since immunization was essentially limited to troops deployed to high-risk areas overseas, the pre-immunization individuals would have been primarily personnel of combat age. In contrast, the never immunized group would have been primarily support personnel and, on average, substantially older. Thus, it is no surprise that the pre-immunized-to-never immunized hospitalization rate ratio is less for diabetes than for all hospitalization diagnoses collectively. One cannot fairly argue that the "never immunized" data is any indication that the

"pre-immunized" rate is artificially depressed.

Table G2 subdivided the post-immunization group into those hospitalized for diabetes within 45 days of immunization (RR 3.49, CI 1.39-8.79) and those so hospitalized more than 45 days after immunization (RR 3.44, CI 1.47-8.06). IOM argued that the similarity of these risk ratios suggested that there was no causal relationship (P.168). However, it is well accepted that type 1 diabetes arises from a chronically progressive autoimmune disease. The vaccine would be expected to accelerate the progression to a clinically recognized disease state. In those adults with extensive destruction of islet cells (from other causes) prior to immunization, diabetes could manifest itself within days or weeks, as in the 0-45 day group. In those adults with no prior damage to their islet cells, diabetes could develop as late as three or more years after immunization (see the "clustering" article, supra).

Indeed, the less than 45 day post-immunization data helps to refute IOM's never/pre argument. If the rise from pre to post had been the result of the artificial depression of the pre data, then why would there be such a rapid response to the immunization?

	IOM concedes that "finding an increased rate of occurrence of one or more adverse events must be considered a signal until proper review provides an alternative explanation." (P. 170)
10. military immunization, US vs. Europe Classen and Classen, "The safety of military immunization and the risk of insulin-dependent diabetes," Clin. Practice Alternative Med., 2:247-252 (2001)	
The US military vaccinates much more extensively than does the European military. Classen found that the risk of IDDM was significantly higher in the US military men than in conscripted European men age 20-35 (RR 1.6, CI 1.45-1.73). In countries where men, not women, are drafted, hence immunized by the military, the men have a significantly higher risk (RR 1.7, CI 1.53-1.84) of developing IDDM than do the women. In the US Navy, where both men and women receive vaccine, the incidence of IDDM is lower in men (RR 0.8, CI 0.64-0.97). The incidence of IDDM in the US Navy increased with age (and hence also with years of exposure to military immunization programs).	This is a newly reported finding.

Table 2A: Critique of Epidemiological Studies Which Reached Conclusion Not Supportive of Applicant (Left col. description of study; right col. applicant's critique.)

1. Moulton (cited by PIDJ)	
PIDJ page 219 col. 2 quotes **unpublished** work by Dr. Larence Moulton to the effect that the rates of incidence of type I diabetes mellitus "in countries where BCG is routinely given at birth or at 1 to 3 months of age are generally lower than the rates where BCG is not given or given at>1 year of age." **This finding supports the present application.** However, PIDJ goes on to refer to "preliminary data from a multiple regression analysis" (presumably also by Moulton) which suggest that "these differences decrease after adjustment for distance from the equator, per capita gross national product, child mortality and per capita caloric intake". PIDJ also argues that "several other factors" could explain the observed differences in diabetes incidence, including "genetic differences in populations and increased exposure to immune modulating infections early in life in tropical climates". (page 219).	To say that the differences "decrease" is not, of course, equivalent to saying that they vanish. Moreover, "preliminary data" is entitled to little weight, especially when it is unpublished and no detailed information (regression coefficients; R2) is given. A recent search on MEDLINE for "Moulton diabetes" found 11 articles meeting the search criterion, none of which appear to be the mysterious multiple regression analysis. Looking at Applicant's data (Appl., page 101), it is striking that Iceland (pertussis, no BCG) had a lower incidence (10.8) than the less northerly, equally developed, equally Caucasian study populations of England (16.4), Northern Ireland (16.6), Scotland (19.8), Denmark (21.5), Norway (20.8), and Finland (42.9) (late immunizations). Moreover, among Southern European states, Italy (6.8, 6.5, 30.2[6]); no pertussis or BCG, France (7.8; pertussis BCG <2 mo) and Portugal (7.5; same) scored lower than Spain (10.6, 10.9; pertussis, no BCG). It should be noted that the countries of Western Europe have relatively high and similar per capita GNP. **Conclusion: The PIDJ review of Moulton's analysis should not be given any weight.**

[6] The very high incidence of diabetes in Sardinian Italy can be explained on a genetic basis, see spec., page 92, lines 18-27.

2. all immunogens, Global LaPorte (cited by PIDJ)	
According to PIDJ, LaPorte presented data "demonstrating a global increase in the incidence of type 1 diabetes mellitus that cannot be explained by improved surveillance." However, PIDJ continues, "the incidence of type 1 diabetes has increased in countries with and without introductions of new vaccines into the immunization schedule." (219, col. 2,- 220, col. 1)	PIDJ does not cite any LaPorte publication as related to this passage. A MEDLINE search revealed Karvonen, et al., "Incidence of Childhood Type 1 Diabetes Worldwide," Diabetes Care, 23: 1516-26 (Oct. 2000). While this article acknowledges that "the incidence of type 1 diabetes appears to be increasing in almost all populations worldwide", it refused to rule out a surveillance effect: Whether this is a true increase resulting from changing lifestyle factors or is simply an improvement in case ascertainment is currently impossible to determine." (1524, col. 2). Also, LaPorte has not presented any of the particulars of this data, i.e., which vaccines were introduced in which countries at which times, what was the immunization protocol, and what was the rate of incidence of diabetes before and after these introductions or protocol changes. PIDJ does not consider whether there are differences in the rate of increase depending on whether a new vaccine had been introduced, or whether changes in old vaccines played any role. A new vaccine administered at birth could decrease incidence, shifting an old vaccine from birth to three months could increase it. Consequently, it is impossible to ascertain the merits of the conclusion stated by PIDJ. **This passage in PIDJ is not entitled to any weight.**

3. BCG-China LaPorte (cited by PIDJ)	
PIDJ declares that "Because BCG vaccine is given to almost all infants at birth in China, Dr. LaPorte noted that the marked variability in the incidence of type 1 diabetes within China is additional evidence against a major effect of BCG on diabetes incidence." (219, col. 2)	PIDJ does not cite any LaPorte publication as related to this passage. A MEDLINE search revealed Yang et al. (LaPorte is a co-author), "Childhood Diabetes in China: enormous variation by place and ethnic group", 21: 525 (1998). This article notes that there is a 12-fold geographic variation and a 6-fold ethnic variation in diabetes incidence in China. It does not make any reference to immunization practices in China. Even if all Chinese were immunized with BCG at birth, it would not be surprising that there is substantial variation in diabetes incidence in a country with "one-fourth of the world's population, 56 ethnic groups spread over 9.6 million square kilometers, and remarkably different climates, diets and patterns of infectious diseases." Applicant claimed that immunization was a risk factor, not that it was the only risk factor, or even the most important one. Nonetheless, Applicant thinks it worth pointing out that Yang et al.'s conclusion was that "China has an extremely low **overall** IDDM incidence rate." Perhaps that is the impact of the BCG immunization at birth.

4. BCG Canada

Parent (1997) cited by PIDJ

Parent (1997) studies the association between BCG immunization and the incidence of IDDM in Quebec. The Montreal paper contains two separate case control studies, series A and B.

Series A pertains to children residing in a particular area of Montreal, born between 1970 and 1976, who were >6 years old at IDDM diagnosis. Controls were matched retrospectively. The authors report that 5 of 93 diabetics had received first BCG immunization when 1-12 years old, as compared to 124 of 2,903 controls (odds ratio of 1.26). Also,, 15 of the diabetics and 499 of the controls received first BCG immunization at "0 years old" (odds ratio 0.94)

Series B contained 249 cases of IDDM (diagnosed from 1982-86, not more than 18 years old; residing in metropolitan Montreal) and 431 prospectively collected matched controls. The authors found 14 of 249 diabetics (31.8% of the vaccinated diabetics) had received first BCG immunization when 1-12 years old, versus 12 of 431 controls (Table 4)(18.4% of the vaccinated controls), yielding an **odds ratio of 2**. In contrast, 30 diabetics received first BCG immunization at "0 years old" (68.2% of the

Use of the Series A data is problematic in that the controls were at least 10 years old (Parent, p.768, col. 3). Classen;s data indicated that the majority of the effect of BCG immunization of IDDM is within 4 years for a school age administration and within 7 years for a birth administration. Hence, the nature of the Series A data was such as would tend to underestimate the incidence of diabetes.

Parent et al.'s original analysis is also of limited relevance here because it did not consider the effect of exact timing of the first dose of BCG vaccine on the development of IDDM. Sufficient data was not available to determine how many children immunized in the first year of life were actually immunized in the first month of life. However, re-analysis of cases and controls immunized starting after 1 year of life with the BCG vaccine indicates the vaccine, thus administered, is associated with an increased risk of IDDM.

Classen has performed a stratified statistical re-analysis, comparing the incidence in children with BCG exposure starting after age 1 to the remaining children, in a dataset combining series A and B. The result was a relative risk of 2.3, with a P value (one tailed) of 0.019. **This is, of course, supportive of the present patent application.** See Classen et al., "Immunization

vaccinated diabetics), as compared to 53 of controls (81.5% of the vaccinated controls), yielding an improved odds ratio (0.98:1). **This result, indicating that the timing of BCG immunization affects diabetes incidence, is consistent with applicant's epidemiological analysis.** Parent noted that "in series B, IDDM occurred at a more advanced age, on average, among vaccinated cases than among those who had not been vaccinated. Moreover, the proportion of cases who developed IDDM by age 5 years was much lower among cases who had been vaccinated at birth than among those who had not been vaccinated." Also, "control subjects were more likely (82% vs. 68%) to be vaccinated at birth than the cases". Parent saw no such difference in series A. Parent conceded that immunization with BCG at birth may have retarded the onset of diabetes. (770, col. 3)	with BCG vaccine starting after age 1 is associated with an increased risk of IDDM in Quebec" (unpublished, copy enclosed).

5. various immunogens, Sweden Blom 1991	
This was a case control study of 339 recently onset diabetic and 528 referent children in Sweden, with the cases of diabetes being those in the 0-14 yr, age group reported 9/1/85-8/31/86. Table 3 shows the odds ratios and confidence intervals for vaccinated diabetic and referent children, for vaccination with tuberculosis, smallpox, tetanus, polio, measles, mumps, rubella, and a combined vaccine including diphtheria. The study reported that measles vaccinations had a statistically significant protective effect against diabetes.	This analysis is likely to underestimate the effect of these commonly used vaccines on the incidence of IDDM because case control studies greatly underestimate the association when there is very high utilization of the vaccine.

6. HBV, Hib, polio, DPT; Colorado Graves (ref. EF)	
A small case-control study of the effect of immunization with HBV, Hib, polio and DPT; the cases were children enrolled in a prospective cohort study in Denver, Colorado. The study examined whether the cases and controls had received any HBV, Hib, Polio or DPT before 9 months, in particular, at birth, and the median age of the first such immunizsation. The study group included 25 cases and 292 controls. No statistically significant differences in rates of incidence between cases and controls were found. The study conceded that both the incidence of diabetes, and the number of different immunogens used in vaccination, have increased over the past 20 years. While the author concluded that changing the immunization schedule would not lower the risk of developing type 1 diabetes, the author hedged by saying that "further case-control studies would be valuable in addressing the lack of data on the effect of immunizations on the risk of developing type 1 diabetes."	This study had several limitations. First, it did not wait for diabetes to actually develop. Graves considered a positive reaction with "at least one autoantibody" to be indicative of diabetes, and it is well known that a single autoantibody has very low specificity for predicting the development of IDDM. Second, Graves studied only 25 individuals with an autoantibody and 292 controls. Graves' study group has only found 5 antibody positive children who developed IDDM. In summary, her study was too small, follow up too short, and markers too nonspecific to consistently make the findings seen by Classen for Finland However, even with all these limitations, Graves found the Hib vaccine associated with an odds ratio of 1.64 which is even greater than the relative risk of 1.19 (166/140) found with the Hib vaccinated children by age 5 in Finland According to Graves, 72% of the 25 cases (receiving any Hib before 9 months; median age of first Hib was 2 months) and only 61% of the 292 controls developed autoantibodies. While this result, by itself, was not statistically significant (p=0.275), its results can be pooled with Applicant's studies which did reach statistical significance. The HBV, polio and DTP studies were also underpowered (10-25 cases, 108-292 controls).

7. Nine immunogens, 7 European centers/countries EURODIAB (ref. EB)	
A seven center collaborative study looked for an association between vaccines and the development of IDDM (Paterson, 2000). The case-control study involved 900 diabetic children and 2,302 controls. The data was collected for children who registered for school in Austria (Vienna), Latvia, Lithuania, Luxembourg, Romania (Bucharest), United Kingdom (Leeds, Northern Ireland) in the period 1989-95 (varies from country to country). The authors calculated odds ratios for nine common vaccinations (tuberculosis, polio, tetanus, diphtheria, pertussis, rubella, measles, mumps, Hib) before and after adjustment for possible confounding variables (center, age group, breast feeding, birth weight, maternal age, jaundice at birth, asthma, and vitamin D supplementation). The unadjusted odds ratios ranged from 0.89 (pertussis) to 1.20 (tetanus), and the adjusted ratios from 0.75 (Hib) to 1.56 (tetanus). The best P value was 0.13, for the adjusted odds ratio (1.27) for rubella. The authors concede that "the hypothesis that early exposure to infections can reduce the risk of diabetes has advocates" (citing Rook et al. and Kolb et al.) and that "there is clear evidence to support it from animal	This study did not make any attempt to distinguish between early and late immunization. Since Applicant's thesis is that early immunization decreases the risk and late immunization increases it, this logically would be expected to blur the relationship between the timing of immunization and the risk of type 1 diabetes. The data shows the hemophilus vaccine was associated with a Relative Risk of 1.16 which is consistent with the statistically significant effect of the Hemophilus vaccine on the incidence of IDDM in a cohort study from Finland (Classen & Classen, 1999). Because of the high level of utilization of the Hemophilus vaccine, a large study group would be needed to detect an effect of this magnitude. The EURODIAB study was underpowered. The diphtheria, tetanus, measles, rubella and polio vaccines were also associated with an increased risk of IDDM though not statistically significant alone. Again, the high rate of uptake of the vaccine in both cases and controls made it unlikely that an effect would be seen with a study of this size. The combined effect of the vaccines was associated with a relative risk of 1.7.

models." They also concluded that early perinatal infections are risk factors for childhood onset of type 1 diabetes. However, they concluded that "vaccinations do not exert any major modifying effect on the risk".	
8. Hepatitis B, USA De Stefano (ref. DU)	
A US government funded study (DeStefano et al., 1997) analyzed data from three HMOs in the USA for about 160,000 children born 1991-95. It concluded that the hypothesis that HepB vaccination at "birth" (more accurately, 0-21 days after birth) decreases IDDM risk was not supported by the data. De Stefano was unwilling to rule out the possibility that hepB vaccination, particularly at older ages, may increase IDDM risk.	The reported relative risk (RR) was 1.3 for those first vaccinated at 0-21 days of age and 1.9 for those first vaccinated at eight weeks or later. Thus, later first immunization was associated with a higher RR, and any immunization increased risk. In a more recent paper (DeStefano, et al., Pediatrics, 108: __, Dec., 2001), the reported RR is 0.51 for those first vaccinated at 0-14d, 0.53 for 15-55d, and 0.86 for 56 or more days. Thus, while later first immunization was associated with a higher RR, any immunization decreased risk. In both studies, the calculated RR was not statistically significant. It is difficult to do case-control studies of vaccines in the US where there are so many vaccines given and there is variability in what is given when, leading to confounding effects. Children who received the hepatitis B vaccine at birth may have been more likely to receive other new vaccines like the Hib vaccine, the chickenpox vaccine, etc., which, depending on their timing, may have increased the risk of diabetes. (In contrast, in Europe, there is much more uniformity in immunization schedules for a given country

	at a given time.) DeStefano did not adjust for the possible confounding effects of other immunizations. While the RR observed in this study was not, by itself, statistically significant, De Stefano's data may be pooled with Applicant's New Zealand data, which showed a statistically significant increase in diabetes incidence following HepB immunization.
9. BCG, Sweden 1973-77 Dahlquist (ref. HK)	
Dahlquist and Gothefors (1995) examined the effect of BCG vaccination in Sweden. Before 1975 all newborns were offered BCG vaccination in the first month of life. In view of the side effects of the vaccine, general BCG vaccination was halted on 1 April 1975. Since then, only high risk groups were given BCG. In 1976, only 0.6% were vaccinated, and in 1976-80, only 2%. Dahlquist examined the cumulative incidence of childhood IDDM in Sweden in children 4-15 yrs old born in 1973-1977. There was no formal statistical analysis, but eyeballing the plot of cumulative incidence against age of diagnosis for the four cohorts, Dahlquist concluded that there was "clearly no significant difference". Dahlquist's cohort data, taken or derived from	A reanalysis of the data (Classen and Classen, Diabetologia, 39:500-501 (1996)(ex. 5A) indicates that BCG immunization at birth was associated with a clinically significant reduction in IDDM. Dahlquist et al. fail to consider the confounding effect of the discontinuation of the smallpox vaccine in 1976.The smallpox vaccine was administered in Sweden primarily at 2 months or 9 months of age as compared to the BCG vaccine which was administered at birth. Data from NOD mice and human ecological studies show that vaccines administered starting after 2 months of life increase the incidence of IDDM thus having the opposite effect of administering vaccines at birth (Classen & Classen, 1997). The Swedish data needs to be analyzed in a way to compensate for the confounding effect of the smallpox vaccine. Swedish law until early 1976 required immunization with smallpox vaccine prior to the age of 5. Unfortunately good records on the acceptance rates in the birth cohorts are not available. Swedish public

the caption to his Fig. 1, was

1973 345 320.69 (107,582)
1974 329 302.75 (108,671)
1976 342 351.39 (927,327)
1977 320 336.49 (95,098)

(year, # cases, rate per 100,000, cohort size)

health officials have indicated that the smallpox vaccine was being increasingly withheld in anticipation of the discontinuation of the law, as it became apparent to physicians that the risk of children developing adverse responses from immunization exceeded the risk of being infected with smallpox. Data from the Netherlands showed this trend clearly. In the Netherlands the smallpox vaccine was given around 9 month of age and was mandatory by age 1 before the law was repealed on November 28, 1975. The acceptance rates by age 1 in the Dutch birth cohorts of 1970-1975 were 88%, 87%, 82%, 66%, 47%, and 9% respectively.

Table 1 of the reanalysis examines the differences between the birth cohorts which received BCG, 1973-1974, and those that didn't, 1976-1977. Dahlquist and Gothefors' analysis which ignores the effect of the smallpox vaccine is listed as assumption A. Three additional assumptions were considered. The most appropriate way to compensate for the confounding effect of the smallpox vaccine would be to compare the middle (1974 and 1976) cohorts (assumption C), If so, the difference in cumulative incidence between cohorts is then 48.64 cases/100,000, with a highly significant one tail P value of 0.0057. This is consistent with the effect of BCG at birth reported by Classen, 52.8 cases/100,000. Even if one compares 1973-74 with 1975-6 (assumption A), there is still a 32.22/100,000 difference, with 1 tailed P value of 0.0363.

10. DTP Sweden Heijbel (Ref. EI)	
The effect of the DTP vaccine on IDDM was studied in Sweden (Heijbel et al., 1997). The study involved comparing the cumulative incidence of IDDM in birth cohorts that received a DTP vaccine lacking an aluminum adjuvant (1977 and 1978 birth cohorts) to birth cohorts receiving a DT vaccine containing an aluminum adjuvant (birth cohorts 1980 and 1981). Both groups appeared to have a similar rate of IDDM.	The analysis was flawed because the MMR vaccine was started at about the same time that the pertussis vaccine was discontinued in Sweden. The 1977 and 1978 birth cohorts which received the pertussis vaccine did not receive the MMR vaccine at 18 months. The 1980 and 1981 birth cohorts which did not receive the pertussis vaccines but did receive the MMR vaccine. Thus the results indicate the pertussis vaccine had an effect similar to the addition of the MMR vaccine; the latter is consistently associated with a relative risk of approximately 1.2. Furthermore, based on the study it is not possible to distinguish the effect of the aluminum adjuvant from the pertussis vaccine. Therefore one can not make a conclusion on the effect of the pertussis vaccine on IDDM. It is likely that both the aluminum adjuvant and the pertussis vaccine increase the risk of diabetes because both are immune stimulants.

11. various immunogens, Auckland, New Zealand Elliott (ref. IJ)	
This abstract reports informally on the incidence of type 1 diabetes in the Auckland area (North Island, New Zealand) over a 20 year period. The authors report "no change in vaccination program involving any one vaccine could be associated with a change in diabetes incidence although the total number of vaccines used could."	The problem with the North Island data is that the population is more transient, and the population has risen in the Auckland area, making the data less accurate than the South Island (personal communication R. Elliott). However, the trend is the same as with the South Island. Elliott's cohort data is set forth in Table 3B of Classen, "Scientific Evidence Proving Vaccines Cause Type I IDDM (June 2000)(of record). This notes that HepB immunization began in 1988, that the average incidence of diabetes in the 1977-87 cohorts was 9.8/100,000, and that the average incidence in the 1989-96 cohorts was 13.3, yielding a relative risk of 1.36. In view of the unreliability of Elliott's data, Applicant does not believe that it should be used to quantify the risk. Nonetheless, the increase carries the implication that HepB immunization, as practiced in Auckland, increases the risk of diabetes.

12. Anthrax, U.S. Armed Forces[7] Institute of Medicine, *The Anthrax Vaccine: Is It Safe? Does It Work?* (March, 2002), available online from the National Academy Press, http://www.nap.edu/books/0309083095/html/	
Anthrax vaccine was given to 150,000 service members deployed for the Gulf War (1991). Later, DOD announced a plan for the mandatory vaccination of all U.S. service members. The program (AVA) began in March, 1998 with personnel sent to high-risk areas, such as South Korea and Southwest Asia. The vaccine is administered in a series of six subcutaneous injections. Obviously, the first administration was no earlier than the minimum age for military service. One of the IOM studies of this program, comparing rates of disorders post- and pre-immunization, has already been discussed. I turn now to consideration of the other IOM studies.	A large study of hospitalized personnel (2,651 vaccinated; 151,609 unvaccinated) apparently did not find an increased RR for diabetes. However, as pointed out previously, the study was inherently flawed because it used unvaccinated personnel as controls. Since only individuals being deployed to high risk areas were vaccinated, and healthy individuals would be preferentially deployed, the unvaccinated personnel would tend to less healthy and more likely to develop diabetes, leading to underestimation of the risk of diabetes attributable to vaccination. Two small studies both reported an increased RR for diabetes, albeit not statistically significant by themselves. The Air Combat Command Study (5,177persons) found a relative risk of 1.68 (0.20-13.9) for ambulatory care visit for diabetes (vaccinated vs. unvaccinated). The Army Aviation Epidemiology Study (3,356 matched pairs of vaccinated and unvaccinated air crew personnel) found a relative risk of 1.25 (0.34-4.66) of diabetes. While these studies were underpowered to detect diabetes risk of the magnitude expected as a result of Applicant's work, they were superior in design to the larger study because they used matched controls.

[7] This reference presents several studies, one of which reports that vaccination significantly increases the risk of diabetes, and others which do not. The favorable study is discussed here and the other studies in Table 2A.

Table 2B: Secondary Sources Cited by the Examiner

Secondary sources are those which do not present any new data or analysis of their own, but merely comment on the work of others.

PIDJ	see discussion of Moulton, LaPorte, Blom, Willis, Graves and Parent in Tables 1 and 2A
Hiltunen (ref. EL) Hiltunen et al. wrote a paper (Hiltunen et al., 1999) pertaining to vaccines and IDDM, claiming that there is no clear evidence that immunization is associated with insulin dependent diabetes (IDDM).	They simply failed to cite animal toxicity studies (Classen, 1996) and epidemiology studies (Classen & Classen, 1997) which show immunization starting after 2 months is associated with an increased risk of IDDM.
Karvonen, Cepaitis, Tuomilehto (ref. EV)	This is an alternative interpretation of the data listed previously as Hib/Finland/Classen and hence is discussed in Table 1.
Bedford (ref. HD) Bedford and Elliman (Bedford & Elliman, 1999) wrote "The workshop panel (May 1998, Johns Hopkins University) concluded that the analytical methods were incorrect. Furthermore, data were available from Professor Tuomilehto showing that follow up over 10 years showed no difference in the incidence of diabetes between children who had received one dose of vaccine and those who had received four doses. The workshop panel examined evidence from several sources and concluded that "there is no evidence that any vaccines have increased the risk of type 1 diabetes in animals or humans."	There was no consensus at the JHU meeting. Panel members at the meeting, were asked to sign a consensus statement refuting an link between vaccines and IDDM but they refused. With respect to the reference to Tuomilehto's data, this is the same Hib/Finland data presented in Karvonen (ref. EV), which is interpreted differently by Classen and by Karvonen. We have already explained why the comparison of the one dose and four dose regimens was inappropriate.

Jefferson,. (HP) In this 1999 letter to BMJ, Jefferson, Rabinovich, and Tuomilehto not only questioned Classen's analysis of the Finland data, see Karvonen (ref. EV), but also asserted that the conclusion of the NIH workshop, presented in June 1998, was that studies in humans do not indicate an increase in type 1 diabetes attributable to any vaccine or the timing of immunisation. "	There was no consensus at the NIH meeting; no vote was taken.
Jefferson (ref. EQ) This is a review paper (Jefferson & Demicheli, 1998) claiming that there is no evidence vaccines cause insulin dependent diabetes (IDDM).	This conclusion must be placed in context; Jefferson declared that "international analytical literature is insufficent and of limited coverage to shed light on the possible link between onset of IDDM and vaccination." So it is unclear why he thought he could state any conclusion. Jefferson's conclusion was seemingly based solely on epidemiological data, with no consideration given to animal studies. Having been published in 1998. it necessarily fails to consider the epidemiological data of Classen and Classen (1999), and later publications with similar findings. Jefferson does not provide any details of his analysis and hence it is unclear how Classen's earlier studies are weighted against that of Blom and Hejbel.

Willis PIDJ ref. 49	Not an independent study, but rather a critique of a Classen study. Hence, it is discussed above in that context.
Petousis-Harris (ref. HE)	not an independent study, but a critique of Classen's New Zealand study, see above.
CDC (ref. IN) This anonymous fact sheet is critical of Classen's animal and epidemiological evidence. With regard to the animal data, it argues that many of the animal experiments included anthrax, which is rarely used in infants and children, and more generally that there are uncertainties in extrapolating from animals to humans. It criticizes some of the epidemiological studies as related to vaccines not used, or only infrequently used, in the USA (smallpox, BCG). It also questions intercountry analysis as potentially affected by many factors. In response to Classen's HIB/Finland analysis, it argues that his results are "inconclusive because the exact number of children in each group is not known and the noted differences may not be statistically significant."	Classen's animal experiments were not limited to use of anthrax, and an immunogen can be given early just for its antidiabetic effect, not to control an infectious disease. The animal tests, moreover, are only part of the supporting evidence; they cannot be viewed in isolation from the human epidemiological data. Whether or not smallpox or BCG are used in the USA, it is relevant to the issue of utility whether the timing of administration of those immunogens has an effect on the incidence of juvenile diabetes. The CDC comments on Classen's Hib/Finland analysis are out-of-date; the Classen 2002 paper provides the number of children in each group, and shows the existence of a statistically significant effect.

11. Several of the studies report a relative risk for immunization that is higher than 1.0, i.e., that immunization increases risk, but the statistical significance (p value) for the individual study is greater than the conventional cutoff value of 0.05. However, that does not mean that the study should be ignored. First of all, the higher relative risk value would be considered in the art to be a signal that the effect should be further evaluated, preferably in a higher powered study. Secondly, it is possible to pool several studies together in order to increase the power of the studies to detect a true effect. Without providing a formal meta-analysis here, it should be noted that in virtually every study of the effect of immunization on diabetes, the relative risk was greater than 1.0. If there were no real effect, one would expect that about half of the studies would report a relative risk of less than 1.0.

12. Natural infections are known to increase the risk of type 1 diabetes. This is presumably attributable the the immune system response to the immunogens presented by the infectious organisms. Vaccination, like infection, exposes the immune system to immunogens. Hence, the disclosed effect of vaccination on diabetes risk is consistent with the known effect of infection on diabetes risk.

It should be noted that the autoimmune effect of vaccination is likely to be considerably greater than the autoimmune effect of infection. For example, vaccines often include potentiating agents (adjuvants), and exposure is typically to a large bolus of immunogen at one, rather than the more gradual exposure typical of a pathogen reproducing on the surface of a mucous membrane. The adrenal gland can increase production of corticosteroids, to suppress an autoimmune response, but this takes about three days, and hence is better suited to control of infection-induced autoimmunity than of immunization-induced autoimmunity. See Classen and Classem, "Vaccines and the risk of insulin-dependent diabetes (IDDm): potential mechanism of action, Medical Hypotheses, 57(5); 532-38 (2001).

13. The physician's package insert for Merck & Co., Inc.'s M-M-R II vaccine (measles, mumps and rubella immunogens) lists both diabetes mellitus and systemic lupus erythematosus (SLE) as adverse reactions "reported during clinical trials, with use of the marketed vaccine, or with use of monovalent or bivalent vaccine containing measles, mumps, or rubella."

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and

further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

John B Classen 10/17/02

J. Barthelow ("Bart") Classen Date

Exhibit List for Classen Declaration (II)

Classen and Classen, "The Timing of Pediatric Immunization and the Risk of Insulin-Dependent Diabetes Mellitus", Infectious Diseases in Clinical Practice (IDCP), 6: 449-54 (1997) (ref. GQ, February 1, 2001 IDS)

Classen and Classen, "Immunization in the First Month of Life may Explain Decline in Incidence of IDDM in The Netherlands," Autoimmunity, 31: 43-5 (1999) (ref. GO)

Classen and Classen, "Diabetes Epidemic Follows Hepatitis B immunization program," New Zealand Med. J., 109: 195 (1996) (ref. DQ).

Classen and Classen, "Clustering of Cases of Insulin Dependent Diabetes (IDDM) Occurring Three Years After Hemophilus Influenza B (Hib) Immunization Support Causal Relationship Between Immunization and IDDM", Autoimmunity, 35(4):247-53 (2002)(published version of unpublished manuscript submitted August 17, 2001)

Classen and Classen, "Association between type 1 diabetes and Hib vaccine: causal relation is likely", BMJ 319:1133 (10/23/99)(ref. HR)

Sanjeevi, et al., Ann. N.Y. Acad. Sci. 958: 293-6 (2002) (newly submitted)

Classen et al., "Immunization with BCG vaccine starting after age 1 is associated with an increased risk of IDDM in Quebec" (unpublished) (newly submitted)

Table 3B of Classen, "Scientific Evidence Proving Vaccines Cause Type I IDDM (June 2000) (Exhibit to December 19, 2000 amendment)

Drykoningen, et al., "The incidence of male childhood type 1 (insulin-dependent) diabetes mellitus is rising rapidly in the Netherlands, Diabetologia, 35: 139-42 (1992) (ref. DX, February 1, 2001 IDS)

Yang et al., "Childhood Diabetes in China: enormous variation by place and ethnic group", 21: 525 (1998) (newly submitted)

Karvonen, et al., "Incidence of Childhood Type 1 Diabetes Worldwide," Diabetes Care, 23: 1516-26 (Oct. 2000) (newly submitted)

DeStefano, et al., "Childhood Vaccinations, Vaccination Timing, and Risk of Type 1 Diabetes Mellitus," Pediatrics, 108: ??, Dec., 2001) (newly submitted)

Institute of Medicine, *The Anthrax Vaccine: Is It Safe? Does It Work?* (March, 2002), available online from the National Academy Press,
http://www.nap.edu/books/0309083095/html/
(selected pages provided: 1, 3, 136-39, 160-64, 166-70,246-48) (newly submitted).

Classen and Classen, "Vaccines and the risk of insulin-dependent diabetes (IDDM): potential mechanism of action, Medical Hypotheses, 57(5); 532-38 (2001). (newly submitted)

Classen and Classen, "The safety of military immunization and the risk of insulin-dependent diabetes," Clin. Practice Alternative

Med., 2:247-252 (2001)

Classen and Classen, Clustering of cases of IDDM occurring 2-4 years after vaccination is consistent with clustering after infections and progression to IDDM in autoantibody positive individuals" (unpublished manuscript). (newly submitted)

The 1999 physician's package insert for Merck & Co., Inc.'s M-M-R II vaccine (9265206), pages 7 and 9. (newly submitted)

Analyses of Sample Size Requirements for Unmatched Case-Control Studies with 90% or 95% Exposure in NOT ILL group. (newly submitted)

Classen and Classen, "Vaccines modulate IDDM," Diabetologia, 39:500-501 (1996)(ref. GP)